REMARKS / ARGUMENTS

Status of the Claims

Upon entry of the attached RCE (Request for Continued Examination), and entry of the amendments presented in the response dated April 7, 2008, claims 12 and 28-52 are pending, and claims 1-11 and 13-27 are canceled.

Support for Amendments

Details of the support for the previously-presented amendments can be found in the response dated April 7, 2008. Support for the amendments was discussed in the Interview of August 6, 2008, and confirmed in the Examiner's Interview Summary mailed August 13, 2008. Applicants understand that the issue of new matter raised in the Advisory Action of June 11, 2008, has been withdrawn, as detailed in the Examiner's Interview Summary mailed August 13, 2008. No new matter is added.

Interview Summary

Applicants' representatives thank the Examiner for the courtesy of a telephone interview on August 6, 2008, as confirmed in the Interview Summary mailed August 13, 2008. Agreement was reached with respect to the withdrawal of the issue of new matter raised in the Advisory Action of June 11, 2008. Agreement was not reached with respect to the pending rejection under 35 U.S.C. § 103(a).

Foreign Priority

The present application is a national phase application of PCT patent application PCT/GB00/01857, filed May 15, 2000 and claims priority to:

(1) GB 9911183.3, filed May 13, 1999,

(2) GB 9911346.6, filed May 14, 1999,

(3) GB 9927005.0, filed November 15, 1999,

(4) GB 9918534.0, filed August 5, 1999,

(5) GB 9927106.6, filed November 16, 1999, and

(6) GB 0007637.2, filed March 29, 2000.

In the Office Action dated November 9, 2007, the Examiner withdrew the prior acknowledgment of Applicants' claim of priority to these foreign applications and determined that the earliest effective filing date for the claims is May 15, 2000 based on the range of about 500 to about 1650 micrograms/m^2 body surface area. Applicants respectfully traverse in view of the amendments submitted in the response dated April 7, 2008.

Applicants note that GB 9911183.3, filed May 13, 1999 includes an Example disclosing that 10 patients received a dose of 1500 $\mu g/m^2$ of Et 743 as a 24 hour continuous infusion every three weeks, with two partial responses, two minor responses, and three stabilizations. In addition, GB 9911346.6, filed May 14, 1999 includes an Example disclosing that patients received doses of 1500 $\mu g/m^2$ or over of Et 743 during 24 hour continuous infusions, and partial responses, a minor response, and stabilizations were observed. Therefore, the claims are entitled to the priority dates of GB 9911183.3 and GB 9911346.6.

With regard to GB 9918534.0, filed August 5, 1999, the disclosure indicates infusion times of up to 24 hours, 2-12 hours, 12-24 hours, and 3 hours are disclosed on page 2.

Intervals of 2 to 4 weeks are disclosed on page 2. In one example, 11 patients were treated at a dose of 1500 $\mu g/m^2$ or over of Et 743 during 24 hour infusions. Six partial responses, one minor response, and 4 stabilizations were observed. Therefore, the claims are entitled to the priority date of GB 9918534.0.

With regard to 9927106.6, filed November 16, 1999, the disclosure indicates infusion times of up to 24 hours, 2-12 hours, 12-24 hours, 2-6 hours, and 3 hours are disclosed on page 2. Intervals of 2 to 4 weeks are disclosed on page 3. Disclosed dosage includes 1500 $\mu g/m^2$ of Et 743 on the page entitled "Ecteinascidin-743 (ET-743) in heavily pretreated refractory sarcomas: early results of the French experience." Four partial responses, 3 minor responses, and 7 disease stabilizations were reported. Therefore, the claims are entitled to the priority date of GB 9927106.6.

Objection to the Disclosure

The Office Action dated November 9, 2007, objects to the disclosure for failing to spell out the acronym for Et 743, and states that Ecteinascidin-743 should be recited at its first occurrence in the independent claim. As required by the Office Action, claim 12 is amended to spell out the acronym for Et 743. In addition, the specification is objected to for failing to provide proper antecedent basis for the term "about" in claims 12 and 15. The objection is moot in view of the amendments presented in the response dated April 7, 2008. Applicants request withdrawal of the objection.

Rejection Under 35 U.S.C. 112, 1st paragraph

The Office Action dated November 9, 2007, rejects claim 14 for lack of written description. By the amendment presented in the response dated April 7, 2008, claim 14 is canceled. Applicants respectfully request withdrawal of the rejection.

Rejection Under Provisional Obviousness Double-Patenting

The Office Action dated November 9, 2007, provisionally rejects claims 12-17 and 24-35 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of co-pending U.S. Patent Application Serial No. 10/492,320. Applicants traverse on the basis that the claims for US 10/492,320 are directed to administration of Et 743 infused over 3 hours at a dosage below 650 micrograms/m^2/week. In addition, because the rejection is provisional, Applicants respectfully request that the rejection be held in abeyance pending the determination of patentable subject matter. Applicants suggest that if all other rejections are overcome, it is appropriate to withdraw the provisional double-patenting rejection and allow the instant application to issue, as directed by the MPEP:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. (MPEP §804).

The Office Action dated November 9, 2007, provisionally rejects claims 12-17 and 24-35 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of co-pending U.S. Patent Application Serial No. 10/579,251. Applicants traverse on the basis that the claims for US 10/579,251 are directed to administration

of the combination of Et 743 and doxorubicin. In addition, because the rejection is provisional, Applicants respectfully request that the rejection be held in abeyance pending the determination of patentable subject matter. Applicants suggest that if all other rejections are overcome, it is appropriate to withdraw the provisional double-patenting rejection and allow the instant application to issue, as directed by the MPEP:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. (MPEP §804).

Rejection Under 35 U.S.C. § 112, second paragraph

The Office Action dated November 9, 2007, rejects claims 13-17 and 24-35 under 35 U.S.C. § 112, second paragraph, as being indefinite due to the term "about" in the claims. Applicants respectfully traverse. However in order to advance prosecution, the term is removed from the claims by the amendment presented in the response dated April 7, 2008. Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 103(a)

The Office Action dated November 9, 2007, rejected claims 12-17 and 24-35 under 35 U.S.C. § 103(a) for being unpatentable over both Taamma et al. (Eur. J. Cancer, 1997) and Riofrio et al. (23rd European Society for Medical Oncology Congress, abstract, 1998) in view of Goodman&Gilman (1996). In the response dated April 7, 2008, Applicants traversed the rejection on the basis that the combination of Taamma, Riofrio, and Goodman&Gilman did not render obvious the claims as amended on April 7, 2008. However, the Advisory Action dated

June 11, 2008 denied entry of the amendments, and maintained the previous rejection of record for the previous set of claims. Specifically, the Advisory Action stated

> Taamma and Riofrio teach each limitation of claim 12. The Goodman & Gilman reference is applied merely to show the administration of dexamethasone is well established in the prior art as an effective antiemetic agent. Motivation to combine the Riofrio document flows from its disclosure drawn to an effective dosage range of ET-743 and to various tumor types that are responsive to ET-743 therapy. There is a clear reasonable expectation of success because the beneficial administration of ET-743 is taught by Taamma.

(Advisory Action, page 3, lines 17-21). Finally, the Interview Summary dated August 13, 2008 stated with respect to the claimed element wherein said treatment results in a reduction in tumor size that "such result would have been a fundamental, expected component of treatment of solid tumors" (Interview Summary, page 4, lines 6-7). Applicants respectfully traverse.

As amended, claim 12 is directed to a method of treatment of a human patient for cancer comprising administering Ecteinascidin-743 (Et 743) at a dose level of 1500 micrograms/m^2 body surface area in cycles by intravenous infusion at intervals of 3 to 4 weeks with an infusion time of 24 hours wherein said treatment results in a reduction in tumor size. In Example 2, two patients had partial responses, where a partial response in oncology is generally understood[1] as approximately 50% tumor shrinkage, measured as the sum of the products of the two longest diameters, or as an overall 30% tumor shrinkage, measured as the sum of the longest diameters. In Example 3, four patients had partial responses, two of which became post-surgical complete responses (i.e., leading to no evidence of disease), and three people had minor responses (one of which became a post-surgical complete response).

[1] See, for example, the guidelines of the World Health Organization, the Response Evaluation Criteria in Solid Tumors, or other established criteria approved by the Protocol Review Committee of the Cancer Therapy Evaluation Program.

In contrast, none of the cited references teach that treatment results in a reduction in tumor size. On the contrary, Taamma fails to report any results at all. Taamma merely teaches that 11 patients were entered in a phase I study. Moreover, Taamma fails to provide any information on dosing levels. Similarly, while Riofrio discloses dosing levels, the reference fails to report any efficacy, let alone any reductions in tumor size. Rather, Riofrio reports nausea and vomiting (grade 2) and transaminase elevation starting 2-4 days after treatment from 600 micrograms/m^2 DL. Finally, Goodman&Gilman is cited for its discussion of dexamethasone as an effective antiemetic in cancer chemotherapeutic regimens. As such, Goodman&Gilman as cited in the Office Action fails to remedy the deficiencies of Taamma and Riofrio in that it lacks any data with respect to Et 743. For at least the reason that the references cited by the Examiner fail to teach or suggest all the claim elements, Applicants request that the rejection be withdrawn.

While Applicants have shown a reduction in tumor size in their invention as claimed, the Office Action has improperly found the previously-presented claims obvious through hindsight reconstruction using Applicants' own data. For example, in response to previous arguments for the previously presented claims, the Interview Summary of August 13, 2008 states that for the required element of a reduction in tumor size, "such result would have been a fundamental, expected component of treatment of solid tumors" (Interview Summary, page 4, lines 6-7). Applicants respectfully traverse this position on the basis that in the field of oncology, phase I trials are not expected to have a "fundamental, expected component of treatment of solid tumors" as stated in the Office Action. In fact, phase I oncology trials have been criticized for providing patients a poor prospect of benefit in exchange for the potential of severe harm (see Horstmann et al., "Risks and Benefits of Phase I Oncology Trials, 1991 through 2002," New England Journal of Medicine, volume 352, issue 9, pages 895-904; March 3, 2005,

page 896, left column, lines 12-15). Published reviews report that a tumor response occurs only in about 4 to 6 percent of the participants in phase I oncology trials while about 0.5 percent of the participants die as a result of toxicity. *Ibid*, lines 9-12, and reference cited therein. In fact, some practitioners in the field of oncology "contend that the enrollment of patients with advanced disease in risky research studies with little chance of direct benefit exploits a vulnerable population. *Ibid*, lines 15-18. The poor ratio of response rate to death is affirmed by Horstmann's analysis of trials from 1991 through 2002, which found an overall response rate of 4.4 percent for "classic phase I" (i.e., single-agent) chemotherapy studies (Horstmann, page 899, left column, lines 28-30). Notably, these poor response rates include disease stabilization, which is understood as neither partial response nor disease progression. According to Horstmann, phase I trials do not have a "fundamental, expected component of treatment of solid tumors" as argued in the Office Action; rather, Horstmann teaches that "factors other than response rates and toxicity should be taken into account" when considering phase I oncology trials (see Horstmann, page 903, paragraph bridging left and right columns). As taught by Horstmann and as understood in the oncology arts, phase I trials are not expected to provide reduction in tumor size. On the contrary, the benefits from phase I trials may be measured in "reduced pain, increased appetite, energy, and activity, weight gain, reduced fatigue, or increased ability to perform daily activities" (Horstmann, page 903, right column, lines 1-5). Therefore, the conclusion of the Office Action, that phase I trials may automatically be considered to have "fundamental, expected component of treatment of solid tumors," is not supported by the literature in the field of oncology. Rather, the literature cautions those in the field such as oncologists, investigators, and members of institutional review boards, to be "aware of the complexity and variety of such trials" (Horstmann, page 904, left column, lines 9-15).

In view of the teachings in the literature in the field of phase I oncology trials regarding complexity, variety, and the generally poor outcomes for patients in phase I oncology trials, Applicants submit that the Office Action has failed to show a reasonable expectation of success in the claimed method based on the cited references, either alone or in combination. Therefore, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Based on the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105002.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105002.

Respectfully submitted,
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